IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Stanley T. Crooke**	Confirmation No.: **4628**
Application No.: **10/281,349**	Group Art Unit: **1635**
Filing Date: **October 25, 2002**	Examiner: **Sean McGarry**

For: **OLIGORIBONUCLEOTIDES AND RIBONUCLEASES FOR CLEAVING RNA**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY PURSUANT TO 37 CFR § 1.111

In response to the Official Action dated **December 11, 2007**, reconsideration is respectfully requested in view of the amendments and/or remarks as indicated below:

☐ **Amendments to the Specification** begin on page of this paper.

☒ **Amendments to the Claims** are reflected in the listing of the claims which begins on page 2 of this paper.

☐ **Amendments to the Drawings** begin on page of this paper and include an attached replacement sheet.

☒ **Remarks** begin on page 6 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-42. (Canceled)

43. (Currently Amended) A method for specifically cleaving a preselected target messenger RNA, comprising

~~(a)~~ contacting ~~said~~ the preselected target messenger RNA with ~~an~~ a single-stranded oligomeric compound and a double stranded ribonuclease, wherein the single stranded oligomeric compound comprises ~~comprising~~ an oligonucleotide consisting of 17 to 25 linked nucleosides wherein:

~~said~~ the oligonucleotide is specifically hybridizable with ~~said~~ the preselected target messenger RNA;

~~said~~ the oligonucleotide comprises at least one sugar modified nucleoside, wherein the modification improves the affinity or specificity of ~~said~~ the ~~compound to said~~ oligonucleotide for the preselected target messenger RNA or increases the resistance of ~~said~~ the oligonucleotide ~~compound~~ to single-stranded nucleases, or both; and

~~said~~ the oligonucleotide comprises a plurality of nucleosides comprising a 2'-hydroxyl pentofuranosyl sugar moiety~~; and~~

~~(b) contacting said preselected RNA and oligomeric compound with a double-stranded nuclease and thereby specifically cleaving said preselected target RNA~~.

44. (Currently Amended) The method of claim 43 wherein ~~said~~ the oligonucleotide comprises at least four consecutive nucleosides comprising 2'-hydroxyl pentofuranosyl sugar moieties.

45-93. (Canceled)

94. (Currently Amended) The method of claim 43, wherein ~~said~~ the oligonucleotide comprises at least two[,] nucleosides comprising 2' sugar modifications.

95. (Currently Amended) The method of claim 94 wherein ~~said~~ the at least two 2' sugar modifications are on consecutive nucleosides.

96. (Currently Amended) The method of claim 94 wherein the at least two 2' sugar modifications are each independently selected from fluoro, C1-C20 alkoxy, C1-C9 aminoalkoxy, allyloxy, imidazolylalkoxy ~~or~~ and polyethylene glycol.

97. (Previously presented) The method of claim 96 wherein the C1-C20 alkoxy modification is 2'-O-methoxyethyl or 2'-O-methyl.

98. (Currently Amended) The method of claim 94 wherein ~~said~~ the at least two 2' modifications are at the 5' or 3' terminal regions of ~~said~~ the oligonucleotide.

99. (Currently amended) The method of claim 94 wherein the ~~terminal~~ 3' terminal four nucleosides of the oligonucleotide each comprise a 2' sugar modification.

100. (Currently amended) The method of claim 94 wherein the ~~terminal~~ 3' terminal five nucleosides of the oligonucleotide each comprise a 2' sugar modification.

101. (Currently amended) The method of claim 94 wherein the ~~terminal~~ 3' terminal six nucleosides of the oligonucleotide each comprise a 2' sugar modification.

102. (Currently amended) The method of claim 94 wherein the ~~terminal~~ 3' terminal seven nucleosides of the oligonucleotide each comprise a 2' sugar modification.

103. (Currently amended) The method of claim 94 wherein the ~~terminal~~ 3' terminal eight nucleosides of the oligonucleotide each comprise a 2' sugar modification.

104. (Currently amended) The method of claim 94 wherein the four 5'-most nucleosides and the four 3'-most nucleosides of ~~said~~ the oligonucleotide each independently ~~comprises~~ comprise a 2' sugar modification.

105-134. (Canceled)

135. (Previously presented) The method of claim 94 wherein the nucleosides comprising 2'-hydroxyl pentofuranosyl sugar moieties are positioned between two segments comprising nucleosides comprising 2'sugar modifications.

136. (Currently amended) The method of claim 43 wherein ~~said~~ the oligonucleotide comprises at least one internucleoside bond that is more stable to degradation as compared to a phosphodiester bond.

137. (Currently amended) The method of claim 136 wherein ~~said~~ the internucleoside bond is phosphorothioate.

138. (Previously presented) The method of claim 137 wherein each internucleoside bond is phosphorothioate.

139. (Currently amended) The method of claim 43 wherein ~~said~~ the oligonucleotide comprises at least one nucleoside comprising a 2'-fluoro modification.

140. (Currently amended) The method of claim 43 wherein ~~said~~ the oligonucleotide comprises four to twelve consecutive nucleosides each comprising a 2'-hydroxyl pentofuranosyl sugar moiety.

141. (Currently amended) The method of claim 44 wherein ~~said~~ the oligonucleotide comprises five to nine consecutive nucleosides each comprising a 2'-hydroxyl pentofuranosyl sugar moiety.

142. (Currently amended) The method of claim 43 wherein ~~said~~ the oligonucleotide consists of 17 to 20 linked nucleosides.

143. (Currently amended) The method of claim 102 wherein ~~said~~ the seven ~~terminal~~ 3' terminal nucleosides comprising a 2' sugar modification each ~~comprises~~ comprise a 2' fluoro.

144. (Canceled)

145. (Currently amended) The method of ~~claim 144~~ claim 143 wherein ~~said~~ each internucleoside linkage of the ~~said~~ oligonucleotide is a phosphorothioate internucleoside linkage.

146-189. (Canceled)

REMARKS

Following entry of the foregoing amendments, claims 43, 44, 94-104, 135-143, and 145 will be pending. Claims 43, 44, 94-96, 98-104, 136, 137, 139-143, and 145 have been amended to more clearly describe the claimed invention. Support for the amendments is found throughout the specification as filed. Thus, the amendments do not introduce new matter into the application. Claims 144 and 146-189 are canceled without prejudice. No new claims have been added.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Claim Objections

Claims 146 and 160 were objected to for containing typographical errors. Those claims have been canceled without prejudice. Thus, the objection is moot.

Alleged Obviousness

Claims 43, 44, 94 to 98, 136 to 142, and 146 to 158 were rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by U.S. patent number 6,087,484 (Goodchild). To advance prosecution, claims 146 to 158 have been canceled without prejudice. Thus, the rejection as applied to those claims will not be discussed. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 43, 44, 94 to 98, and 136 to 142, because Goodchild fails to teach or suggest every limitation of those claims.

To establish *prima facie* obviousness, the Patent Office must demonstrate that the cited prior art reference or combination of references teaches or suggests all of the limitations of the claims. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Independent claim 43 recites methods for specifically cleaving a preselected target messenger RNA comprising contacting the target messenger RNA with a single-stranded oligomeric compound and a double stranded RNase, wherein the single-stranded oligomeric

compound comprises an oligonucleotide consisting of 17 to 25 linked nucleosides that comprises at least one sugar modified nucleoside and a plurality of nucleosides comprising a 2'-hydroxyl pentofuranosyl sugar moiety. Goodchild does not teach methods of using oligomeric compounds having the recited combination of modifications or number of nucleosides.

Goodchild teaches use of "facilitator oligonucleotides," which reportedly hybridize to a target nucleic acid adjacent to a ribozyme binding site to improve cleavage by the ribozyme. None of the facilitator oligonucleotides specifically disclosed in Goodchild falls within the scope of the present claims. For example, claim 43 recites oligonucleotides that comprise at least one sugar modified nucleoside and a plurality of nucleosides comprising 2'-hydroxyl pentofuranosyl sugar moieties. None of the facilitator oligonucleotides specifically disclosed in Goodchild comprises such modifications. In fact all of the compounds disclosed in Goodchild are either unmodified RNA or DNA or are uniformly modified. For example, the oligonucleotides of Example 4 are either all RNA, all DNA, or all 2'-O-Me. Although Goodchild remarks that "facilitator oligonucleotides are preferably synthesized to comprise from one to all modified nucleotides, which can be ribonucleotides, deoxyribonucleotides, or a combination thereof,"[1] in fact, Goodchild does not specifically disclose any facilitator oligonucleotides having a combination of modifications. Moreover, the generalized remark that oligonucleotides may be some combination of modified nucleosides does not provide sufficient guidance to render obvious the particular combination claimed. Indeed, such a statement provides no more than a general suggestion to "vary all parameters or try each of numerous possible choices until one possibly arrives at a successful result" and further lack "any direction as to which of many possible choices is likely to be successful." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 83 USPQ 2d 1289, 1305 (Fed. Cir. 2007), [citing *In re O'Farrell*, 853F.2d 894, 903 (Fed. Cir. 1988)]. For at least that reason, Claim 43 is not obvious in view of Goodchild.

Furthermore, none of the compounds specifically disclosed in Goodchild contain "17 to 25" nucleosides as recited in claim 43. The facilitator oligonucleotides disclosed in Goodchild are all 16 nucleosides in length or shorter. The only discussion of facilitator oligonucleotides

[1] Id at col. 2-3.

longer than 16 nucleosides in length is the broad statement that "facilitator oligonucleotides of the present invention typically comprise between about 5 and 50 nucleotides."[2] However, the discussion continues, "More preferred facilitator oligonucleotides comprise between about 5 and 15 nucleosides. Particularly preferred facilitators according to the invention comprise about 10-15 nucleosides."[3] Thus, Goodchild provides only generalized teachings of longer oligonucleosides insufficient to render obvious the present claims.

As discussed above, Goodchild provides no reason why one of ordinary skill in the art would prepare an oligonucleotide having at least one sugar modified nucleoside and a plurality of nucleosides comprising 2'-hydroxyl pentofuranosyl sugar moieties. Further, Goodchild provides no reason why one of ordinary skill one would prepare an oligonucleotide that is longer than 16 nucleosides. And Goodchild certainly provides no reason why one of ordinary skill in the art would prepare an oligonucleotide that is *both* longer than 16 nucleosides *and* has the claimed modifications. For at least those reasons, Goodchild fails to render obvious claim 43. The remaining claims all ultimately depend from claim 43. Thus, those claims are likewise non-obvious. The Office has failed to establish *prima facie* obviousness and Applicants accordingly, respectfully request withdrawal of the rejection.

Alleged Indefiniteness

Claims 99 to 104 and 143 to 145 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Office asserted that antecedent basis does not exist in claims 99 to 103 for the phrase "the terminal…nucleosides" because it would allegedly be unclear to those skilled in the art which terminus of the oligonucleotide the claims refer to. Without conceding the correctness of the assertion, and to advance prosecution, claims 99 to 103 have been amended to recite the phrase "3' terminal," obviating the rejection. Support for the amendments is found throughout the specification as originally filed, including, for example, page 9, lines 17

[2] Id at col. 3.
[3] Id.

to 37; page 18, lines 8 to 12; page 24, line 33 to page 25, line 18; and page 31, line 33 to page 32, line 6. The amendments thus do not introduce new matter into the application.

Claim 145 was rejected as allegedly indefinite for recitation the phrase "said each internucleoside linkage," which the Office asserts lacks antecedent basis. To advance prosecution, claim 143 has been amended to recite "each internucleoside of the oligonucleotide." Claim 145 ultimately depends from claim 43, which recites an "oligonucleotide consisting of 17 to 25 linked nucleosides." Internucleoside linkages are inherent in an oligonucleotide consisting of linked nucleosides. The rejection has thus been obviated, and applicants accordingly, respectfully, request withdrawal thereof.

Alleged Insufficiency of the Written Description Provided in the Specification

Claims 43, 44, 94 to 104, 135 to 189 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. To advance prosecution, claims 144 and 146 to 189 have been canceled without prejudice. Thus, the rejection as applied to those claims will not be discussed. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 43, 44, 94 to 104, 135 to 143, and 145.

The Office contends that the claims "contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Office Action at page 6. Specifically, the Office asserts that written description is not satisfied because, the "specification does not provide a description of what this protein's [dsRNAse] structure is, but only a method of isolating it." Office Action at page 6. The Office cites several cases in support of the view that structure is required. See, e.g., Office Action at pages 1-9 (citing Freirs v. Revel; Fiddes v. Baird; and University of California v. Eli Lilly). Applicants respectfully submit that application of these cases to the present claims is inapt.

Rejected claim 43 recites methods for specifically cleaving a preselected target RNA, comprising contacting the target RNA with certain oligomeric compounds and a double-stranded ribonuclease. Thus, the claim is not directed to an isolated or purified dsRNase, as suggested by

the rejection and as was the case in each of the cited cases. Cases and discussion describing what written description may be necessary to claim an isolated protein or nucleic acid is simply not relevant to the present claims. Instead, the standard is whether one of skill in the art would appreciate that the Applicants were in possession of the invention as claimed at the time of filing. The Office has failed to articulate any reason why written description demands structural description of every feature of a method claim and Applicant is unaware of any such requirement.

Moreover, while the present rejections are unlike those in the cases cited by the Office, they are, instead similar to those found to satisfy the written description requirement in *In re Fuetter*.[4] In that case, the claims were drawn to a rubber stock composition useful in producing tire treads and included recitation of "an inorganic salt capable" of maintaining a homogeneous distribution of another component in the composition.[5] The specification described the desired function for the inorganic salt and included four salts having that function. The *Fuetter* court held that the written description requirement was satisfied for methods using any inorganic salt, because the claims were directed to a combination that included an inorganic salt, rather than to the salt itself, and stated the following:

> Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure.[6]

[4] 319 F.2d 259 (C.C. P.A.1963)
[5] *Id.*
[6] *Id.*

Similarly, claims in *In re Herschler* were drawn to methods of enhancing the penetration of "a steroid" across a membrane comprising concurrent administration with DMSO.[7] The board upheld a rejection for lack of written description because the specification exemplified only a single species of steroid, corticosteroid.[8] In reversing the board, the court held that the written description was sufficient to support the claimed methods noting that:

> use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description.[9]

The court emphasized that written description did not require detailed description of each steroid because the applicants were not claiming the steroids themselves.

Likewise, the present claims are not directed to double strand ribonucleases, but rather, recite methods for cleaving a target RNA that include the step of contacting target RNA with an oligomeric compound and a double stranded ribonuclease. As articulated by the *Herschler* and *Fuetter* courts, description in the specification of the necessary functionality of enzymes that can be utilized in the claimed methods and of one or more species of such enzymes is sufficient to satisfy the written description requirement. The present specification teaches that use of certain oligomeric compounds results in cleavage of target RNA, as claimed.[10] The specification describes the necessary functionality of the double stranded RNases with particularity and specificity such that those skilled in the art would readily appreciate that applicants were in possession the claimed methods at the time of filing.

Finally, the Office cites a post-filing publication and asserts that the "claimed invention requires the use of a vast range of ds RNases, where subsequent work has shown that the description provided in the instant specification is inadequate to practice the invention as broadly as claimed." Office Action at page 7. The Office suggests that post-filing publications

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[7] *Id.* at page 695.
[8] 591 F.2d 693, 697 (C.C.P.A. 1979), copy attached as Appendix A
[9] *Id.* at page 702.
[10] Page 13, lines 11 to 16.

identifying additional embodiments of an invention will determine whether the invention was adequately described at the time of filing. Written description must be assessed as of the time of filing. The alternative, as suggested by the Office, is not only contrary to law and precedent, but creates an untenable situation where Applicants cannot know whether an invention is adequately described until years later when post-filing art can be assessed. Fortunately, the law makes no such demand.

For at least the above reasons, Applicants submit that claims 43, 43, 44, 94 to 104, 135 to 143, and 145 are fully supported by the specification as filed. Applicants respectfully request reconsideration and withdrawal of the rejection under § 112, first paragraph.

Conclusion

Applicant believes that the foregoing constitutes a full and complete response to the Office Action of record. An early and favorable action is therefore respectfully requested.

Respectfully submitted,

Date: May 22, 2008

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LEXSEE 591 F2D 693

IN THE MATTER OF THE APPLICATION OF ROBERT J. HERSCHLER

Appeal No. 78-548.

United States Court of Customs and Patent Appeals

591 F.2d 693*; *1979 CCPA LEXIS 313*; *200 U.S.P.Q. (BNA) 711

February 1, 1979, Decided; As Amended

PRIOR HISTORY: **[**1]** Serial No. 304,283.

CASE SUMMARY:

PROCEDURAL POSTURE: Appellant sought review of decision of the Patent and Trademark Office Board of Appeals affirming the rejection of claims 1-5 and 9-13 in appellant's patent application.

OVERVIEW: Appellant sought review of a decision affirming the rejection of claims 1-5 and 9-13 in his patent application. The court reversed, holding that affidavits sufficiently established that the inventor of the great-grandparent application and the inventor of the application on appeal were identical. Purported co-inventor of the great-grandparent application was originally joined through error and without deceptive intent. The court also held that the array of information supplied in the great-grandparent application would teach one having ordinary skill in the art that one of the class of steroids would operate in the claimed process. One having ordinary skill in the art would find use of the subgenus of steroids to be apparent in the written description of the great-grand parent application. Finally, the court held that information supplied in earlier references would not have provided impetus or knowledge to one skilled in the art, such as appellant, to use DMSO in order to enhance penetration of steroidal agents though a membrane.

OUTCOME: The court reversed the rejection of appellant's application. Affidavits established that the inventor of the great-grandparent application and the inventor of the application on appeal were identical. Information in earlier references would not have provided impetus or knowledge to one skilled in the art to use DMSO in order to enhance penetration of steroidal agents though a membrane.

LexisNexis(R) Headnotes

Patent Law > Claims & Specifications > Description Requirement > General Overview
Patent Law > Jurisdiction & Review > Subject Matter Jurisdiction > Appeals
[HN1] The function of the description requirement is to ensure that the inventor had possession of, as of the filing date of the application relied upon, the specific subject matter later claimed by him; how the specification accomplishes this is not material.

Patent Law > Claims & Specifications > Description Requirement > General Overview
Patent Law > Jurisdiction & Review > Subject Matter Jurisdiction > Appeals
[HN2] The claimed subject matter need not be described in haec verba to satisfy the description requirement.

Patent Law > Claims & Specifications > Description Requirement > General Overview
Patent Law > Claims & Specifications > Enablement Requirement > General Overview
Patent Law > Jurisdiction & Review > Subject Matter Jurisdiction > Appeals
[HN3] It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations.

Patent Law > Claims & Specifications > Description Requirement > General Overview
Patent Law > Jurisdiction & Review > Subject Matter Jurisdiction > Appeals

[HN4] The written description of a class of compounds must provide a measure of predictability for the utility described for that class.

Patent Law > Claims & Specifications > Description Requirement > General Overview
Patent Law > Claims & Specifications > Enablement Requirement > General Overview
Patent Law > Jurisdiction & Review > Subject Matter Jurisdiction > Appeals
[HN5] Claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description.

COUNSEL: *Stanley M. Teigland,* attorney of record, for appellant.

Joseph F. Nakamura for the Commissioner of Patents, *Fred W. Sherling,* Associate Solicitor, *Ernest G. Therkorn,* of counsel.

[Oral argument on October 3, 1978 by Stanley M. Teigland for appellant and by Ernest Therkorn for the Patent and Trademark Office]

OPINION BY: BALDWIN

OPINION

[*694] Before RICH, BALDWIN and MILLER, Associate Judges, and KASHIWA * and FORD, ** Judges.

* The Honorable Shiro Kashiwa of the United States Court of Claims, sitting by designation.

** The Honorable Morgan Ford of the United States Customs Court, sitting by designation.

BALDWIN, Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Appeals (board) affirming the rejection of claims 1-5 and 9-13 in appellant's application serial No. 304,283, [1] filed November 6, **[*695]** 1972, for "Enhancing Tissue Penetration of Physiologically Active Steroidal Agents with DMSO." [2]

1 This application is a division of serial No. 69,155, filed September 2, 1970, now U.S. 3,711,606, which in turn is a continuation-in-part of serial No. 753,231, filed August 16, 1968, now U.S. 3,551,554, which is a continuation-in-part of application serial No. 329,151 (hereafter the "great-grandparent"), filed December 9, 1963, now abandoned.

2 **[**2]** Dimethyl sulfoxide (hereinafter DMSO) is a water-clear, water-miscible, hygroscopic, neutral organic liquid, melting at about 18 degree C. and boiling at about 189 degree C. It is a well-known industrial solvent represented by the following formula:

	O	
	"	
CH 3	S	CH 3

The board affirmed the examiner's rejection of all claims under *35 USC 103* as unpatentable over Lubowe in view of Faust, Marson or Brown. The board also affirmed a rejection, first entered pursuant to its authority under 37 CFR 1.196(b), [3] of each of the claims under *35 USC 102(b)* or *103* over Stroughton et al., Stroughton or Kligman. [4] We reverse.

3 37 CFR 1.196(b) provides, in pertinent part, that:

> (b) Should the Board of Appeals have knowledge of any grounds not involved in the appeal for rejecting any appealed claim, it may include in its decision a statement to that effect with its reasons for so holding, which statement shall constitute a rejection of the claims.

4 These references were not part of the certified record transmitted to the court. However, appellant admits in his brief that the rejection is proper if the great-grandparent lacks a written description of the invention in issue. The contents of the references need not be considered.

[3]** The Invention

The appellant has found that DMSO enhances the penetration of a number of materials through skin tissue. In the application at hand, a mixture of DMSO and a "physiologically active steroidal agent" is administered to skin (or a mucous membrane) with the result that the steroid penetrates the membrane. The claimed process provides such advantages as the elimination of injection by needle and the ability to administer localized doses of the drug without resort to a systemic dose.

Claim 1 is typical of the invention:

1. A method of enhancing the penetration into and across an external membrane barrier of a human or animal subject of a physiologically active steroidal agent capable of eliciting a physiological effect upon topical application thereof, which comprises the concurrent topical administration to the external membrane of an amount of said steroidal agent effective to produce the desired physiological effect and an amount of DMSO sufficient to effectively enhance penetration of said steroidal agent to achieve the desired physiological effect.

The Prior Art

The following references were relied upon to support the rejection under *§ 103*:

Lubowe *Patent* **[**4]** *No. 2,942,008* issued on June 21, 1960.

Brown et al., "A Note on the Toxicity and Solvent Properties of Dimethyl Sulfoxide," 15 J. Pharm. Pharma. Col. 688-692 (Oct. 1963).

Faust, "Some New Components for Cosmetic and Dermatologic Vehicles," 77 American Perfumer 23-26 (Jan. 1962).

Marson, "I1 Dimetilsolfossido Solvente Aquo-Mimetico," 102 Boll. Chimicofarm. 109-124 (Feb. 1963).

Lubowe is a patent directed to compositions with large amounts of mineral, vegetable or animal oils solubilized in short chain alcohols. The oils are maintained in solution by the addition of fatty alcohols having 10 to 24 carbon atoms. The resulting compositions may be used as a base in a number of further cosmetic and pharmaceutical compositions. When the composition is used in a hair lotion, Lubowe indicates that "estrogenic hormones, methyl sulfoxide" may be added. Example XII shows a hair lotion containing 0.1% estrogenic hormone in 50% ethyl alcohol but without DMSO.

[*696] Brown et al. shows DMSO to be a solvent in which many classes of compounds are soluble and, further, is of low toxicity.

Faust suggests that DMSO is a "safe and effective solubilizing" agent suitable for use **[**5]** as a cosmetic or dermatologic vehicle.

Marson cites Faust saying "the cosmetic literature has recently cited its [DMSO's] employment as simple, non-gelated components of dermatological vehicles" and describes the usefulness of DMSO in preparing pharmaceutical compositions containing, inter alia, the thickening agents such as recited in the claims.

Background

The examiner indicated in the Final Rejection and in his Answer that the claims were rejected under *35 USC 103* since "the Lubowe patent describes, inter alia, DMSO added to Ex. XII, an anti-seborrheic hair lotion containing 1/10 part by weight of estrogenic hormone," and that, "we have, inherently, the same process involved here as described in Lubowe, notwithstanding applicant's observation of percutaneous absorption from the DMSO (apparently added as a vehicle or solvent, according to Faust, Marson or Brown)."

The board, in a first opinion, agreed with the Examiner's position and amplified it, stating:

We note that the secondary references make it clear that DMSO is an effective solubilizing agent for various drugs, including those to be applied topically and along with the examiner we emphasize that "... an amount **[**6]** of DMSO sufficient to effectively enhance penetration..." of the steroid is also an amount effective for solubilization of the steroid; compare with page 19 of the specification. Therefore, we find that it would be obvious to add DMSO to the steroid containing formulation of Example XII of Lubowe in amounts large enough to enhance penetration of said steroid, in view of the teachings of the secondary references regarding DMSO's utility as a solvent for topical drug formulations.

The board made an additional rejection:

Under the provisions of 37 CFR 1.196(b) we make new grounds of rejection under *35 USC 102(b)* and *35 USC 103* against claims 1 to 5 and 9 to 13.

Claims 1 to 5 and 9 to 13 are rejected under *35 USC 102* and *35 USC 103* as unpatentable over any one of Stoughton et al, Stoughton or Kligman. All of the above publications were made of record by appellant's counsel in Paper No. 6 of great-grandparent case Serial No. 329,151 filed December 9, 1963. The above articles were described in detail by appellant's counsel in said Paper No. 6 (pages 8 to 12) and we will not, therefore, elaborate on the disclosure of the articles. It is sufficient to note that each of the articles **[**7]** teaches the enhanced penetration of various steroids resulting from topical application of DMSO concurrently with the ster-

oid--the heart of appellant's inventive concept. All of the above articles were published in 1964 or 1965, more than one year prior to the filing date of appellant's grandparent case Serial No. 753,231, filed August 16, 1968. Hence the articles are statutory bars against the present claims under *35 USC 102(b)* and *103* unless appellant's claimed invention was described in great-grandparent case Serial No. 329,151 filed December 9, 1963; see *35 USC 120* and *35 USC 112*, first paragraph.

We have carefully considered the great-grandparent case but the only disclosure relating to steroids (pages 34-35) is limited to gluco-corticosteroids whereas all of the present claims on appeal are drawn either to steroids in general or to steroids not limited to glucocorticosteroids (claims 4-5). It is now well settled law that disclosure of a species is insufficient to provide descriptive support for a generic or sub-generic claim; *In re Ruscetta et al, 45 CCPA 968, 255 F.2d 687, 118 USPQ 101 (1958)*, *In re Lukach, 58 CCPA 1233, 442 F.2d 967, 169 USPQ 795 (1971)* and *In re Smith,* **[**8]** *59 CCPA 1025, 458 F.2d 1389, 173 USPQ 679 (1972).* **[*697]**

Hence, appellant may not rely upon his great-grandparent case to support any of the claims on appeal and thus the above articles are prior art and can be properly applied against the claims under *35 USC 102(b)* and *103*. We note also that the great-grandparent case was filed in the name of Jacob and Herschler, whereas the present case was filed by Herschler alone. Since the inventive entities are different, we do not see how appellant can claim priority under *35 USC 120* based upon the great-grandparent case; note the requirement that the applications be "... filed by the same inventor...." [Emphasis in original.]

Appellant thereupon submitted a Request for Reconsideration accompanied by two attachments and requested that the examiner consider them. The first attachment was a portion of a 508 page collection of papers given at a conference entitled Conference on Biological Actions of Dimethyl Sulfoxide held by the New York Academy of Sciences in 1974. The second enclosure was a copy of a Rule 45 declaration [5] submitted in the great-grandparent application purporting to amend the inventorship from Jacob and Herschler **[**9]** joint to Herschler sole.

> 5 Rule 45(b) of the Rules of Practice in Patent Cases provided, at the time of the affidavit in issue (1965), that:
>
> (b) If an application for patent has been made through error and without any deceptive intention by two or more persons as joint inventors when they were not in fact joint inventors, the application may be amended to remove the names of those not inventors upon filing a statement of the facts verified by all of the original applicants, and an oath or declaration as required by rule 65 by the applicant who is the actual inventor, provided the amendment is diligently made. Such amendment must have the written consent of any assignee.

In support of the Rule 45 affidavit, appellant argued:

With respect to the first reason, submitted herewith are copies of papers filed under Rule 45 in the great-grandparent application, and a copy of a postcard receipt indicating that the papers were received by the Patent Office. The papers include an amendment under Rule 45 to change **[**10]** the inventorship of the great-grandparent application to correspond to the inventorship of this application. No notice was received that entry of the amendment was refused. Moreover, the Rule 45 papers were filed simultaneously with a continuing application in the name of the new inventorship and the Patent Office accorded continuation-in-part status to the application, which issued as U.S.P. 3,551,554. Hence, it is evident that the examiner considered the papers filed under Rule 45 and acknowledged that they were legally sufficient to change the inventorship. However, if the examiner believes it is necessary to formally change the inventorship of the great-grandparent application, he is invited to enter the Rule 45 amendment nunc pro tunc.

Appellant further argued that the written description in the great-grandparent was adequate for the subgenus now claimed:

As clearly indicated in the great-grandparent application, appellant recognized from the start that the invention was applicable to physiologically active agents in general. * * * Thus, the Board's contention that "the only disclosure [in the great-grandparent application] relating to steroids is limited to glucocorticosteroids" **[**11]** is incorrect. The great-grandparent application discloses that the invention is applicable to the genus of physiologically active agents, which includes the important subgenus of steroids. A working example illustrates practice of the invention with a corticosteroid, which, of course, is a species of the subgenus of steroids. Hence, the great-grandparent application, in teaching the applicability of the invention to the genus of physiologically active agents in general, and to the species corticosteroids in particular, quite naturally describes to one skilled in the art the applicability of the invention to the subgenus of steroids. Since a corticosteroid is obviously a type of steroid, **[*698]** and since the word "corticosteroid" contains the very word "steroid", the corticosteroid in the working example, in view of the applicability of the invention to physiologically active agents in general, clearly represents to one skilled in the art the subgenus of

steroids. There is no other subgenus that it would reasonably represent.

The collection of papers submitted to the New York Academy of Sciences was said to demonstrate that "in view of the interest in DMSO generated by **[**12]** appellant's discovery, as shown by this reference, the discovery was truly a pioneering breakthrough in medical science." And further, that the papers describing work by:

Kligman and others with just a few different species of steroids [show], that DMSO enhances the penetration of steroids in general. This same conclusion would similarly be drawn by one skilled in the art from the disclosure in appellant's great-grandparent application. Thus, the great-grandparent application describes to one skilled in the art the invention claimed in this application.

The board remanded the application to the examiner for consideration of the appended paper. In a supplemental Answer, the examiner stated:

The Examiner respectfully declines the invitation to either now enter, nunc pro tunc, in an abandoned application, or to even consider what precisely Stanley Jacob did, or not, co-invent, in unverified copies of submitted purported Rule 45 amendment papers, which papers, even if not untimely, are unclear: ("various embodiments", "several additional embodiments", "I was informed on July 18, 1968 that I was not a coinventor", etc.), and considers them not relevant or sufficiently precise **[**13]** to any specific issues herein of whether or not he did not in fact co-invent the applicable portions of S.N. 329,151, filed jointly with him, which relate to DMSO topically applied with a species of glucocorticosteroid * * *. [Furthermore, the board expressly states that] "we have carefully considered.", but they found, (and appellant has not denied,) that its only disclosure relating to steroids (pages 34-35) is limited to the single species of glucocorticosteroids, whereas all of the present claims on appeal are drawn either to steroids in general, or to steroids not limited to glucocorticosteroids (claims 4-5), and the Board of Appeal [sic] held it to be now well settled law that disclosure of a species is insufficient to provide descriptive support for a generic or sub-generic claim, citing the Ruscetta et al, Lukach and Smith decisions. Assuming, arguendo, that the precise inventorship of said glucocorticosteroid species and DMSO is established as not involving a different inventorship question; the question remains, for review under *35 USC 141* or *145*, where, in S.N. 329, 151, is described the steroid genus or subgenus, now claimed? [Emphasis in original.]

The application **[**14]** was then returned to the board. Appellant filed another request for reconsideration reiterating the comments and arguments made in the earlier request.

The board's final opinion indicated that:

We agree with the Examiner that the unverified and unclear papers purportedly filed under *37 CFR 1.45* do not establish that the inventorship of 329,151 and that of the instant case are the same.

We have carefully reconsidered our new ground of rejection under *35 USC 102(b)* and *103* over the newly cited art but we are convinced that the rejection is sound. Apart from the different inventive entities of 329,151 and the instant case we remain of the view that there is no description [in] 329,151 of the process as applicable to steroids. In *In re Smith, 178 USPQ 620 (1973)*, there was also a description in the parent case of a broad genus and a particular species, yet the CCPA held that there was insufficient descriptive support for a subgeneric claim similar to the present subgenus claims drawn to steroids. We do not see how an article published in 1974 or 1975 can aid appellant in overcoming the deficiencies in disclosure of an application filed December 9, 1963. **[*699]** The fact **[**15]** remains that nowhere in Serial No. 329,151 is there any mention of the term "steroids," let alone a description of the claimed process as applicable to steroids as a class.

We reiterate our position that claims 1 to 5 and 9 to 13 are obvious over Lubowe in view of any one of Faust, Marson or Brown under *35 USC 103*. We do not agree with appellant that it would not be obvious to solubilize steroids (such as the estrogenic hormone in Example XII of Lubowe) with DMSO. As explained by the Examiner in his answer, the secondary references make it clear that DMSO is an effective solubilizing agent for various drugs, including those to be applied topically. We emphasize again that "... an amount of DMSO sufficient to effectively enhance penetration..." of the steroid is also an amount effective for solubilization of the steroid. We therefore find clear motivation from the teachings of the prior art to solubilize steroids intended for topical application by adding DMSO to steroid formulations in an amount sufficient to solubilize components of the steroid formulation. The fact that appellant may use DMSO for a different purpose (as compared to the prior art teachings that DMSO solubilizes **[**16]** drugs to be applied topically) does not alter the conclusion that its concomitant use with topically applied drugs such as estrogen would be prima facie obvious from the purpose disclosed in the references; *In re Lintner, 173 USPQ 560, 562 (CCPA 1972)*.

OPINION

35 USC 102(b)/103 Rejection over Stroughton et al., Stroughton or Kligman

As noted above, appellant concedes that the substance of this rejection is proper if the court finds either the great-grandparent application lacks a written description of the instant invention [6] or the inventorship of the great-grandparent application differs from the one on appeal. The analysis need only consider those two points.

6 We assume, in the absence of any argument to the contrary, that the parent and grandparent applications contain the necessary written description of the invention on appeal. See *In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973)*.

Rule 45 Affidavit

The board found that the "unverified [7] and unclear papers * * * do not establish **[**17]** that the inventorship of 329,151 and that of the instant case are the same." We do not agree.

7 It is not altogether clear what is meant by "unverified" in referring to the copy of the affidavit submitted to the examiner. The PTO had physical possession of the original affidavit at the time of the board decision as is evidenced by a certified copy thereof in the transcript submitted to the court. Further verification seems unnecessary.

Jacob's affidavit indicated that he learned of the invention from the appellant:

Herschler disclosed at this meeting his conception of the invention of enhancing tissue penetration of physiologically active agents by applying them to animal tissue (both topically and internally) together with DMSO and his reduction to practice of various embodiments of this invention. Herschler requested at this meeting that my group test various additional embodiments of this invention for him.

and that his participation "concerning the invention disclosed and claimed in application **[**18]** Serial No. 329,151 was limited to assisting in further testing of the invention with such additional pharmacologically active agents."

Although the affidavit is somewhat vague regarding specific acts done by the affiant, it is quite clear that he derived all information pertinent to the disclosed invention from Herschler and acted only under Herschler's direction. The affidavit is consistent with a finding that Jacob was not an inventor in the great-grandparent application. The accompanying affidavit of Herschler (ratifying the statement of **[*700]** Jacob), in conjunction with the originally filed application papers, leads us to the conclusion that Herschler believes himself to be the inventor of the matter disclosed and claimed in the great-grandparent application.

This is not to say that we agree with appellant that the inventorship of the great-grandparent application was effectively amended by the PTO's acquiescence in accepting the sole inventorship of the grandparent nor do we agree that the great-grandparent was amended nunc pro tunc by the submission of copies of the Rule 45 papers. We consider the affidavits sufficient, for the purpose of claiming priority under **[**19]** *§ 120*, to demonstrate that Jacob was joined as a coinventor through error without deceptive intent. *Weil v. Fritz, 572 F.2d 856, 196 USPQ 600 (CCPA 1978)*; *In re Schmidt, 48 CCPA 1140, 293 F.2d 274, 130 USPQ 404 (1961)*.

Written Description in the Great-Grandparent

The appealed claims recite a subgenus, i.e., physiologically active steroidal agents, not found in haec verba in the great-grandparent application.

Appellant emphasizes the following quotation found in the great-grandparent specification and argues that it clearly defines a genus to which the subgenus of steroids belongs:

By the term "physiologically active substance" is meant any substance which has a demonstrable and desired physiological activity in the sense that animal tissue responds thereto. This may be an altered physiologic phenomenon following heparin administration; a pharmacological activity such as local anesthesia; an antibacterial activity following administration of antibiotics; a bacteriostatic activity following the administration of iodine; a growth stimulation activity following usual access to dietary sources, and the like. The term is intended to include any desirable pharmacological action **[**20]** with compounds alien to animal tissue, and any physiological activity with compounds normally occurring in animal tissue. It is also meant to include within the term "physiologically active substance" materials which are diagnostic tools such as radiopaque agents (for instance, iodine), dyes and the like.

That application exemplifies a single species within the terms of claim 1 of this appeal:

Example 30

Penetration of Corticosteroids

A twenty-four year old medical student was seen with stopic dermatitis of the right antecubital fossa. Three cc. of 100% dimethyl sulfoxide were applied four times daily for three days. No benefit was noted. One mg. or 1/4 cc. of Decadron (dexamethasone 21-phosphate) was applied four times a day for two days without benefit. One mg. of dexamethasone 21-phosphate in 3 cc. of 100% dimethyl sulfoxide was

painted onto the involved area four times daily for three days. At the end of this period all evidence of the inflammatory reaction had disappeared.

This example shows an improved action of dexamethasone 21-phosphate when used with dimethyl sulfoxide.

No other language in that specification specifically discusses topical application of **[**21]** a steroid-containing composition.

However, the remaining examples are awesome in their diversity. The scope of exemplified "physiologically active substances" includes iodine (Example 1), pressed pellet feed for rats (Example 4), penicillin (Example 10), procaine (Example 16), various chemotherapeutic agents (Examples 17 & 18), barbiturates (Example 19), oral insulin (Example 21), antihistamines (Example 29), various local anesthetics (Examples 34 & 35), etc.

[HN1] The function of the description requirement is to ensure that the inventor had possession of, as of the filing date of the application relied upon, the specific subject matter later claimed by him; how the specification accomplishes this is not **[*701]** material. *In re Smith, 481 F.2d 910, 178 USPQ 620 (CCPA 1973).* [HN2] The claimed subject matter need not be described in haec verba to satisfy the description requirement. *In re Smith, 59 CCPA 1025, 458 F.2d 1389, 173 USPQ 679 (1972).* [HN3] It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations. **[**22]** *In re Smythe, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973).*

The question is simple: does the array of information supplied by appellant in the great-grandparent application teach one having ordinary skill in this art that one of the class of steroids will operate in the claimed process. We conclude that it does.

A toehold on the problem is found in *In re Cook, 58 CCPA 1049, 439 F.2d 730, 169 USPQ 298 (1971).* [HN4] The written description of a class of compounds must provide a measure of predictability for the utility described for that class. That is to say: would the worker of ordinary skill in this art consider "steroidal agents" to be operative when considering the great-grandparent's disclosure? It is incumbent, in the first instance, for the PTO to give reasons why he would not. *In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 98 (CCPA 1976).* The solicitor urges that the class of steroids is so large that a single example in the specification could not describe the varied members with their further varied properties. We disagree with this contention. Steroids, when considered as drugs, have a broad scope of physiological activity. On the other hand, steroids, when considered **[**23]** as a class of compounds carried through a layer of skin by DMSO, appear on this record to be chemically quite similar. The diversity of exemplified materials "potentiated" by DMSO in the great-grandparent application, is much broader than the diversity of steroid compounds shown contemporaneously in the art. [8] In this instance, we conclude that one having ordinary skill in this art would have found the use of the subgenus of steroids to be apparent in the written description of the great-grandparent application.

8 See, e.g., Kirk-Othmer, "Sterols and Steroids," 12 Encyclopedia of Chemical Technology 917-947 (1st Ed. 1954).

Were this application drawn to novel "steroidal agents," a different question would be posed.

We wish to maintain the line first clearly drawn in *In re Fuetterer, 50 CCPA 1453, 319 F.2d 259, 138 USPQ 217 (1963).* There, claims drawn to a rubber stock composition useful in producing tire treads included a recitation of "an inorganic salt capable" of maintaining an homogeneous distribution **[**24]** of another component in the composition. The disclosure listed the function desired and four members of the class having that function. This court found the written description requirement to be satisfied:

Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure.

We are not persuaded that our conclusion on this point is wrong by decisions of this and other courts relating to the sufficiency of invention disclosures in cases wherein the applicant is claiming chemical compounds per se. [Emphasis **[**25]** in original.]

[*702] *Id. at 1462, 319 F.2d at 265, 138 USPQ at 223.* Applications with claims either to intermediate classes of new compounds per se or claims drawn to processes using those new compounds have been considered by this court on other occasions. *In re Driscoll, 562 F.2d 1245, 195 USPQ 434 (CCPA 1977)*; *In re Ruschig, 54 CCPA 1551, 379 F.2d 990, 154 USPQ 118 (1967)*; *In*

re Fried, 50 CCPA 954, 312 F.2d 930, 136 USPQ 429 (1963). The principles stated therein are still alive and well.

In sum, [HN5] claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description. In Fuetterer and here, such is the case.

35 USC 103 Rejection over Lubowe in view of Faust, Marson or Brown

Throughout the Lubowe patent, DMSO is mentioned only once, and that occurs in the statement that DMSO, as well as many other enumerated compounds, may be added to hair lotion preparations containing a solubilized oil. **[**26]** There is no indication of why the DMSO would be added; nor is there any teaching that there is any relationship between DMSO and estrogenic hormones (which are steroids), let alone a suggestion to employ them in combination. The board relies upon the secondary references to show "that DMSO is an effective solubilizing agent for various drugs, including those to be applied topically" and accordingly finds it obvious to utilize DMSO in Lubowe's Example XII. Such a conclusion is not supported by the record, because, as appellant notes, "the formulation of [Lubowe's] Example XII is already a clear solution containing more solvent than anything else. Moreover, the alcohol solvent employed in Lubowe is also a solvent for steroids." Hence, there would have been no reason for one skilled in the art to add any additional solvent to Lubowe's formulations, particularly a totally different solvent "in any amount large enough to enhance penetration," as required by the claims. Nor would it have been obvious to one skilled in the art to substitute DMSO for a portion of the exemplified alcohols, since Lubowe's invention is directed to the use of specific combinations of alcohols in the disclosed **[**27]** formulations.

While the secondary references may teach that DMSO is generally useful as a solvent, there is no suggestion or teaching in any of them to combine it with a steroid--that is, to choose DMSO from among the countless number of solvents as the solvent for steroids.

Appellant argues that Brown, by stating that DMSO is "not known to interfere with absorption or metabolism," is a teaching not to use DMSO. The solicitor, on the other hand, characterizes the same quotation by saying that "it is not clear how this teaching is a teaching away * * * [and, accordingly] there should be no [suprisesic] that DMSO enhances penetration." Even though that quotation from Brown cannot be said to be an overwhelming suggestion to use DMSO for any solvent-type utility, we do not see how it provides any motivation for one skilled in the art to use DMSO in the formulation of Lubowe. The references do not provide any impetus to do what appellant has done nor do they provide the art with the knowledge that DMSO enhances penetration of "steroidal agents" through a membrane. [9]

9 We do not find it necessary to reach the question of the weight to be given the papers presented to the New York Academy of Sciences in that appellant has no prima facie showing of obviousness to rebut. Were such a showing appropriate, these papers could, if properly presented, indicate wide-scale acceptance in the art and provide a secondary consideration capable of overcoming a *§ 103* rejection.

[28]** Summary

We reverse the decision of the board, which decision affirmed a rejection of the claims both under *35 USC 102* and *103*.

REVERSED